

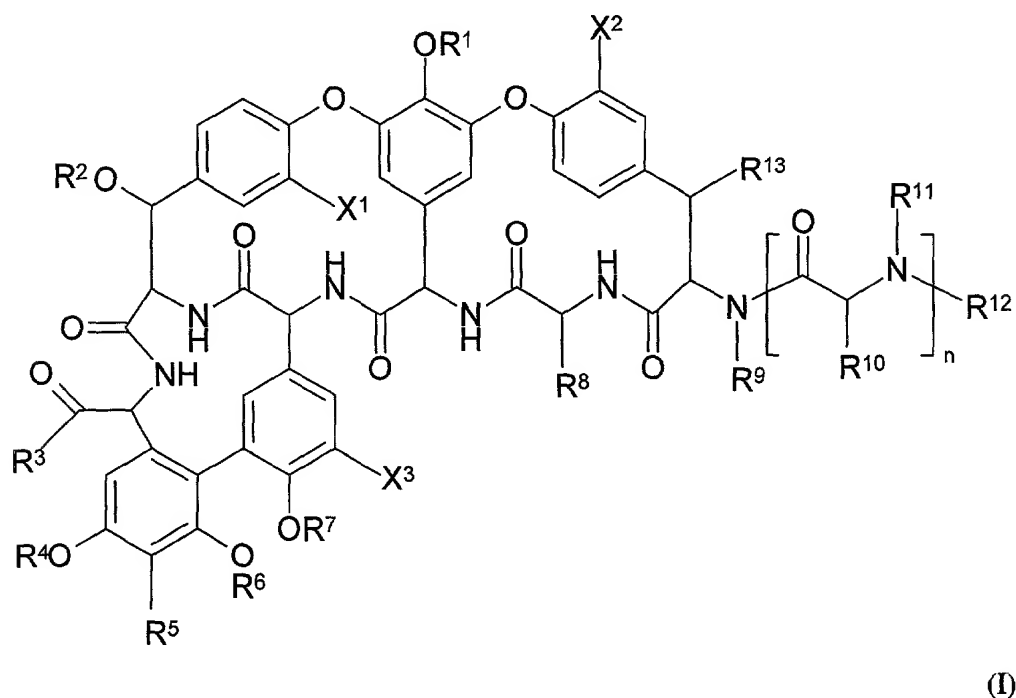
WHAT IS CLAIMED IS:

1. A method for alkylating a glycopeptide that comprises a saccharide-amine comprising:
combining an aldehyde or ketone, a suitable base, and the glycopeptide or a salt thereof, to provide a reaction mixture;
acidifying the reaction mixture; and
combining the reaction mixture with a suitable reducing agent, to provide a glycopeptide that is alkylated at the saccharide-amine.
2. The method of claim 1 wherein the glycopeptide comprises at least one amino group other than the saccharide-amine.
3. The method of claim 2 wherein reductive alkylation at the saccharide-amine is favored over reductive alkylation at the other amino group of the glycopeptide by at least about 10:1.
4. The method of claim 2 wherein reductive alkylation at the saccharide-amine is favored over reductive alkylation at the other amino group of the glycopeptide by at least about 20:1.
5. The method of claim 1 wherein the reductive alkylation is carried out in the presence of a suitable solvent.
6. The method of claim 5 wherein the solvent is a halogenated hydrocarbon, a linear or branched ether, an aromatic hydrocarbon, an alcohol, dimethylsulfoxide, N,N-dimethylformamide, acetonitrile, water, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-

pyrimidone, tetramethyl urea, N,N-dimethylacetamide, diethylformamide, 1-methyl-2-pyrrolidinone, tetramethylenesulfoxide, glycerol, ethyl acetate, isopropyl acetate, N,N-dimethylpropylene urea, or dioxane, or a mixture thereof.

7. The method of claim 6 wherein the solvent is acetonitrile, water, DMF, or methanol, or mixtures thereof.
8. The method of claim 1 wherein the reaction mixture that is combined with the reducing agent comprises a protic solvent.
9. The method of claim 1 wherein the reductive alkylation is carried out at a temperature in a range of about 0 °C to about 50 °C.
10. The method of claim 1 wherein the base is a tertiary amine.
11. The method of claim 1 wherein the acid is a carboxylic acid or a mineral acid.
12. The method of claim 1 wherein the acid is trifluoroacetic acid.
13. The method of claim 1 wherein the reducing agent is sodium cyanoborohydride, sodium triacetoxyborohydride, pyridine/borane, sodium borohydride, or zinc borohydride.
14. The method of claim 1 wherein the reducing agent is a hydrogen source and a transition metal catalyst.
15. The method of claim 1 further comprising isolating the alkylated glycopeptide.

16. A method for preparing an alkylated glycopeptide comprising: combining an aldehyde or ketone, a suitable base, and a compound of formula I:



wherein:

- R^1 is an amino saccharide group;
- 5 R^2 is hydrogen or a saccharide group;
- R^3 is R^3 is $-OR^c$, $-NR^cR^c$, $-O-R^a-Y-R^b-(Z)_x$, $-NR^c-R^a-Y-R^b-(Z)_x$, $-NR^cR^c$, or $-O-R^c$;
- R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, $-C(O)R^d$ and a saccharide
- 10 group;

R^5 is selected from the group consisting of hydrogen, halo, $-\text{CH}(R^c)-\text{NR}^cR^c$, $-\text{CH}(R^c)-\text{NR}^cR^c$, $-\text{CH}(R^c)-\text{NR}^c-R^a-Y-R^b-(Z)_x$, $-\text{CH}(R^c)-R^x$, and $-\text{CH}(R^c)-\text{NR}^c-R^a-\text{C}(=\text{O})-R^x$;

5 R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, $-\text{C}(\text{O})R^d$ and a saccharide group;

R^7 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, and $-\text{C}(\text{O})R^d$;

10 R^8 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^9 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

15 R^{10} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic; or R^8 and R^{10} are joined to form $-\text{Ar}^1-\text{O}-\text{Ar}^2-$, where Ar^1 and Ar^2 are independently arylene or heteroarylene;

20 R^{11} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic, or R^{10} and R^{11} are joined, together with the carbon and nitrogen atoms to which they are attached, to form a heterocyclic ring;

25 R^{12} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic,

$-C(O)R^d$, $-C(NH)R^d$, $-C(O)NR^cR^c$, $-C(O)OR^d$, and $-C(NH)NR^cR^c$, or R^{11} and R^{12} are joined, together with the nitrogen atom to which they are attached, to form a heterocyclic ring;

R^{13} is selected from the group consisting of hydrogen or $-OR^{14}$;

5 R^{14} is selected from hydrogen, $-C(O)R^d$ and a saccharide group;

each R^a is independently selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene;

10 each R^b is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene;

15 each R^c is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and $-C(O)R^d$;

each R^d is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^e is a saccharide group;

20 R^x is a nitrogen-linked amino saccharide or a nitrogen-linked heterocycle;

X^1 , X^2 and X^3 are independently selected from hydrogen or chloro;

25 each Y is independently selected from the group consisting of oxygen, sulfur, $-S-S-$, $-NR^c-$, $-S(O)-$, $-SO_2-$, $-NR^cC(O)-$, $-OSO_2-$, $-OC(O)-$, $-NR^cSO_2-$, $-C(O)NR^c-$, $-C(O)O-$, $-SO_2NR^c-$, $-SO_2O-$, $-P(O)(OR^c)O-$, $-P(O)(OR^c)NR^c-$, $-OP(O)(OR^c)O-$, $-OP(O)(OR^c)NR^c-$, $-OC(O)O-$, $-NR^cC(O)O-$, $-NR^cC(O)NR^c-$, $-OC(O)NR^c-$, $-C(=O)-$, and $-NR^cSO_2NR^c-$;

each Z is independently selected from hydrogen, aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic;

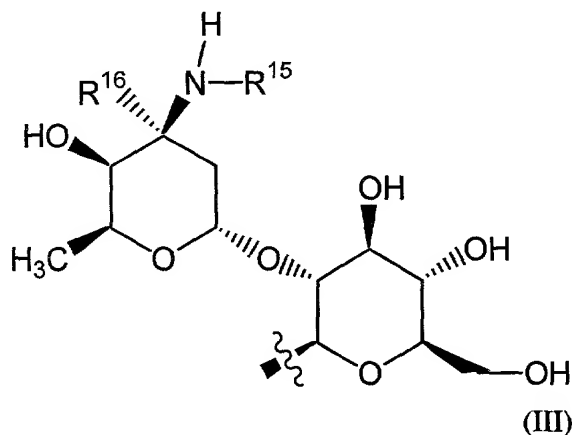
n is 0, 1 or 2; and

x is 1 or 2;

- 5 or a stereoisomer or salt thereof; to provide a reaction mixture;
acidifying the reaction mixture; and

combining the reaction mixture with a suitable reducing agent, to provide the corresponding glycopeptide alkylated at the amino group of the amino saccharide.

17. The method of claim 16 wherein R¹ is an amino saccharide of formula (III):



- 10 wherein R¹⁵ is H; and R¹⁶ is hydrogen or methyl.

18. The method of claim 16 wherein R², R⁴, R⁶, and R⁷ are each hydrogen.

19. The method of claim 16 wherein R³ is -OH.

20. The method of claim 16 wherein R⁵ is hydrogen, -CH₂-NHR^c, -CH₂-NR^cR^e or -CH₂-NH-R^a-Y-R^b-(Z)_x.

21. The method of claim 16 wherein the alkylated glycopeptide is a compound of formula I wherein R^1 is an amino saccharide wherein the saccharide-amine is substituted with $-R^a-Y-R^b-(Z)_x$, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, or substituted cycloalkenyl.

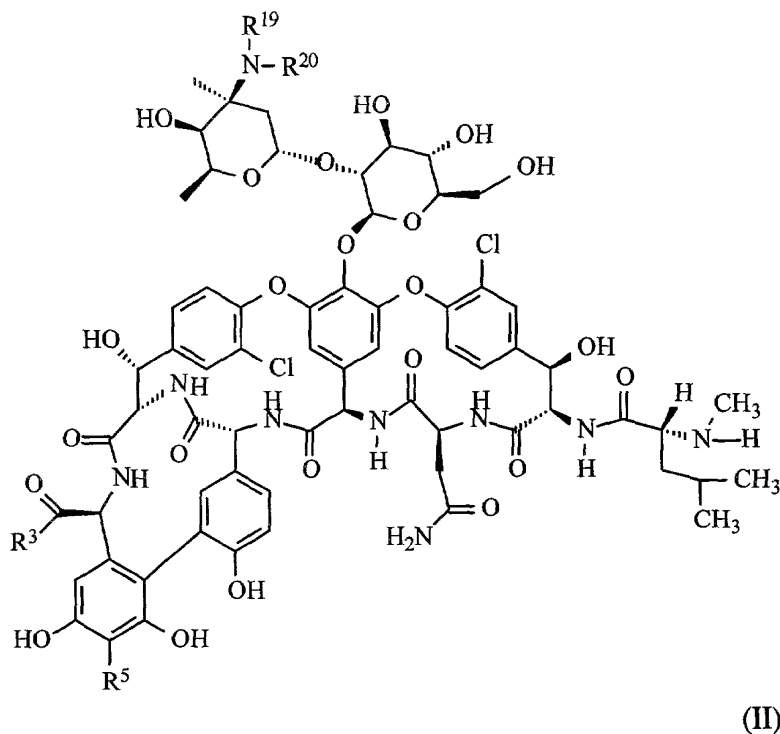
22. The method of claim 16 wherein the alkylated glycopeptide is a compound of formula I wherein R^1 is an amino saccharide wherein the saccharide-amine is substituted with $-\text{CH}_2\text{CH}_2-\text{NH}-(\text{CH}_2)_9\text{CH}_3$; $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{NH}-(\text{CH}_2)_8\text{CH}_3$; $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{NH}-(\text{CH}_2)_7\text{CH}_3$; $-\text{CH}_2\text{CH}_2-\text{NHSO}_2-(\text{CH}_2)_9\text{CH}_3$; $-\text{CH}_2\text{CH}_2-\text{NHSO}_2-(\text{CH}_2)_{11}\text{CH}_3$; $-\text{CH}_2\text{CH}_2-\text{S}-(\text{CH}_2)_8\text{CH}_3$; $-\text{CH}_2\text{CH}_2-\text{S}-(\text{CH}_2)_9\text{CH}_3$; $-\text{CH}_2\text{CH}_2-\text{S}-(\text{CH}_2)_{10}\text{CH}_3$; $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{S}-(\text{CH}_2)_8\text{CH}_3$; $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{S}-(\text{CH}_2)_9\text{CH}_3$; $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{S}-(\text{CH}_2)_3-\text{CH}=\text{CH}-(\text{CH}_2)_4\text{CH}_3$ (*trans*); $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{S}-(\text{CH}_2)_7\text{CH}_3$; $-\text{CH}_2\text{CH}_2-\text{S}(\text{O})-(\text{CH}_2)_9\text{CH}_3$; $-\text{CH}_2\text{CH}_2-\text{S}-(\text{CH}_2)_6\text{Ph}$; $-\text{CH}_2\text{CH}_2-\text{S}-(\text{CH}_2)_8\text{Ph}$; $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{S}-(\text{CH}_2)_8\text{Ph}$; $-\text{CH}_2\text{CH}_2-\text{NH}-\text{CH}_2-4-(4-\text{Cl}-\text{Ph})-\text{Ph}$; $-\text{CH}_2\text{CH}_2-\text{NH}-\text{CH}_2-4-[4-(\text{CH}_3)_2\text{CHCH}_2]-\text{Ph}$; $-\text{CH}_2\text{CH}_2-\text{NH}-\text{CH}_2-4-(4-\text{CF}_3-\text{Ph})-\text{Ph}$; $-\text{CH}_2\text{CH}_2-\text{S}-\text{CH}_2-4-(4-\text{Cl}-\text{Ph})-\text{Ph}$; $-\text{CH}_2\text{CH}_2-\text{S}(\text{O})-\text{CH}_2-4-(4-\text{Cl}-\text{Ph})-\text{Ph}$; $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{S}-\text{CH}_2-4-(4-\text{Cl}-\text{Ph})-\text{Ph}$; $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{S}(\text{O})-\text{CH}_2-4-(4-\text{Cl}-\text{Ph})-\text{Ph}$; $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{S}-\text{CH}_2-4-[3,4-\text{di-Cl-PhCH}_2\text{O}]-\text{Ph}$; $-\text{CH}_2\text{CH}_2-\text{NHSO}_2-\text{CH}_2-4-[4-(4-\text{Ph})-\text{Ph}]-\text{Ph}$; $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{NHSO}_2-\text{CH}_2-4-(4-\text{Cl}-\text{Ph})-\text{Ph}$; $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{NHSO}_2-\text{CH}_2-4-(\text{Ph}-\text{C}\equiv\text{C})-\text{Ph}$; $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{NHSO}_2-4-(4-\text{Cl}-\text{Ph})-\text{Ph}$; or $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{NHSO}_2-4-(\text{naphth-2-yl})-\text{Ph}$.

23. The method of claim 17 wherein the alkylated glycopeptide is a compound of formula I wherein R^1 is a saccharide group of formula III, wherein R^{15} is $-R^a-Y-R^b-(Z)_x$, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl,

substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl.

24. The method of claim 23 wherein R¹⁵ is -CH₂CH₂-NH-(CH₂)₉CH₃;
-CH₂CH₂CH₂-NH-(CH₂)₈CH₃; -CH₂CH₂CH₂CH₂-NH-(CH₂)₇CH₃;
5 -CH₂CH₂-NHSO₂-(CH₂)₉CH₃; -CH₂CH₂-NHSO₂-(CH₂)₁₁CH₃;
-CH₂CH₂-S-(CH₂)₈CH₃; -CH₂CH₂-S-(CH₂)₉CH₃; -CH₂CH₂-S-(CH₂)₁₀CH₃;
-CH₂CH₂CH₂-S-(CH₂)₈CH₃; -CH₂CH₂CH₂-S-(CH₂)₉CH₃; -CH₂CH₂CH₂-S-(CH₂)₃-
CH=CH-(CH₂)₄CH₃ (*trans*); -CH₂CH₂CH₂CH₂-S-(CH₂)₇CH₃;
-CH₂CH₂-S(O)-(CH₂)₉CH₃; -CH₂CH₂-S-(CH₂)₆Ph; -CH₂CH₂-S-(CH₂)₈Ph;
10 -CH₂CH₂CH₂-S-(CH₂)₈Ph; -CH₂CH₂-NH-CH₂-4-(4-Cl-Ph)-Ph;
-CH₂CH₂-NH-CH₂-4-[4-(CH₃)₂CHCH₂-]-Ph; -CH₂CH₂-NH-CH₂-4-(4-CF₃-Ph)-Ph;
-CH₂CH₂-S-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂-S(O)-CH₂-4-(4-Cl-Ph)-Ph;
-CH₂CH₂CH₂-S-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂CH₂-S(O)-CH₂-4-(4-Cl-Ph)-Ph;
-CH₂CH₂CH₂-S-CH₂-4-[3,4-di-Cl-PhCH₂O-]-Ph; -CH₂CH₂-NHSO₂-CH₂-4-[4-(4-
15 Ph)-Ph]-Ph; -CH₂CH₂CH₂-NHSO₂-CH₂-4-(4-Cl-Ph)-Ph;
-CH₂CH₂CH₂-NHSO₂-CH₂-4-(Ph-C≡C-)-Ph; -CH₂CH₂CH₂-NHSO₂-4-(4-Cl-Ph)-Ph;
or -CH₂CH₂CH₂-NHSO₂-4-(naphth-2-yl)-Ph.

25. A method for preparing an alkylated glycopeptide comprising:
combining an aldehyde or ketone, a suitable base, and a compound of formula II:



wherein:

- R^3 is $-OR^c$, $-NR^cR^c$, $-O-R^a-Y-R^b-(Z)_x$, $-NR^c-R^a-Y-R^b-(Z)_x$, $-NR^cR^c$, or
5 $-O-R^c$;
 R^5 is selected from the group consisting of hydrogen, halo, $-\text{CH}(R^c)-NR^cR^c$,
 $-\text{CH}(R^c)-NR^cR^c$, and $-\text{CH}(R^c)-NR^c-R^a-Y-R^b-(Z)$;
 R^{19} and R^{20} are each hydrogen;
each R^a is independently selected from the group consisting of alkylene,
10 substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted
alkynylene;

each R^b is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene;

5 each R^c is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and -C(O)R^d;

R^e is a saccharide group;

10 each Y is independently selected from the group consisting of oxygen, sulfur, -S-S-, -NR^c-, -S(O)-, -SO₂-, -NR^cC(O)-, -OSO₂-, -OC(O)-, -NR^cSO₂-, -C(O)NR^c-, -C(O)O-, -SO₂NR^c-, -SO₂O-, -P(O)(OR^c)O-, -P(O)(OR^c)NR^c-, -OP(O)(OR^c)O-, -OP(O)(OR^c)NR^c-, -OC(O)O-, -NR^cC(O)O-, -NR^cC(O)NR^c-, -OC(O)NR^c- and -NR^cSO₂NR^c-;

15 each Z is independently selected from hydrogen, aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic; and

x is 1 or 2; or a stereoisomer or salt thereof; to provide a reaction mixture; acidifying the reaction mixture; and

20 combining the reaction mixture with a suitable reducing agent, to provide the corresponding alkylated glycopeptide wherein R²⁰ is -R^a-Y-R^b-(Z)_x, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, or substituted cycloalkenyl.

26. The method of claim 25 wherein R²⁰ is -CH₂CH₂-NH-(CH₂)₉CH₃;
-CH₂CH₂CH₂-NH-(CH₂)₈CH₃; -CH₂CH₂CH₂CH₂-NH-(CH₂)₇CH₃;
-CH₂CH₂-NHSO₂-(CH₂)₉CH₃; -CH₂CH₂-NHSO₂-(CH₂)₁₁CH₃;
25 -CH₂CH₂-S-(CH₂)₈CH₃; -CH₂CH₂-S-(CH₂)₉CH₃; -CH₂CH₂-S-(CH₂)₁₀CH₃;
-CH₂CH₂CH₂-S-(CH₂)₈CH₃; -CH₂CH₂CH₂-S-(CH₂)₉CH₃; -CH₂CH₂CH₂-S-(CH₂)₃-

- CH=CH-(CH₂)₄CH₃ (*trans*); -CH₂CH₂CH₂CH₂-S-(CH₂)₇CH₃;
-CH₂CH₂-S(O)-(CH₂)₉CH₃; -CH₂CH₂-S-(CH₂)₆Ph; -CH₂CH₂-S-(CH₂)₈Ph;
-CH₂CH₂CH₂-S-(CH₂)₈Ph; -CH₂CH₂-NH-CH₂-4-(4-Cl-Ph)-Ph;
-CH₂CH₂-NH-CH₂-4-[4-(CH₃)₂CHCH₂-]-Ph; -CH₂CH₂-NH-CH₂-4-(4-CF₃-Ph)-Ph;
5 -CH₂CH₂-S-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂-S(O)-CH₂-4-(4-Cl-Ph)-Ph;
-CH₂CH₂CH₂-S-CH₂-4-(4-Cl-Ph)-Ph; -CH₂CH₂CH₂-S(O)-CH₂-4-(4-Cl-Ph)-Ph;
-CH₂CH₂CH₂-S-CH₂-4-[3,4-di-Cl-PhCH₂O-]-Ph; -CH₂CH₂-NHSO₂-CH₂-4-[4-(4-
Ph)-Ph]-Ph; -CH₂CH₂CH₂-NHSO₂-CH₂-4-(4-Cl-Ph)-Ph;
-CH₂CH₂CH₂-NHSO₂-CH₂-4-(Ph-C≡C-)-Ph; -CH₂CH₂CH₂-NHSO₂-4-(4-Cl-Ph)-Ph;
10 or -CH₂CH₂CH₂-NHSO₂-4-(naphth-2-yl)-Ph.

27. The method of claim 1, further comprising preparing a pharmaceutically acceptable salt of the alkylated glycopeptide.
28. The method of claim 1, further comprising, combining a pharmaceutically acceptable carrier with the alkylated glycopeptide to provide a pharmaceutical composition.
- 15 29. The method of claim 27, further comprising, combining a pharmaceutically acceptable carrier with the salt, to provide a pharmaceutical composition.